propiolactone, a non-ionic detergent which is n-octyl-α-D-glucopyranoside or n-octyl-β-D-glucopyranoside, and ascorbic acid, to provide a non-infectious, non-immunopotentiating and protective RS viral preparation, and

formulating said non-infectious, non-immunopotentiating and protective RS viral preparation as a vaccine.

CH cancel

15. (Amended) A method of immunizing a host against disease caused by respiratory syncytial virus, which comprises administering to the host an effective amount of the vaccine [immunogenic] composition of claim 1.

Amend line 1 of each of claims 3 and 4 to change the numeral "2" to read "1".

Amend line 1 of claim 11 to change the numeral "10" to read "5".

Cancel claims 2 and 10.

REMARKS

Petition is hereby made under the provisions of 37 CFR 1.136(a) for an extension of two months of the period for response to the outstanding Office Action on this case. We enclose our cheque in the amount of the prescribed fees.

In the Office Action, the Examiner has repeated several grounds of rejection from the prior Office Action and has referred to several passages from the prior Office Action. The Examiner has indicated, in some instances, that the applicant's arguments are not commensurate in scope with the claim language, in that applicant's arguments were directed to vaccines, whereas the claims were directed to the preparation and provision of an immunogenic composition. Having regard to the Examiner's comments in this regard, applicant's claims now have been limited to a vaccine and a method of preparation of a vaccine, the vaccine comprising a purified respiratory syncytial (RS) viral preparation, which is free from cellular

and serum components and which is non-infectious, non-immunopotentiating, immunogenic and protective.

As was previously stated, for many years, the production of an RS virus vaccine has been hampered by the adverse effects produced with a formalin-inactivated RS virus in a human clinical trial conducted in the United States in the 1960's. In view of these results, the efforts of vaccine producers in the last 30 years have concentrated on the production of live attenuated RS virus mutants or subunit vaccines, rather than the use of inactivation. Various review articles of record herein relating to the RS virus quite clearly demonstrate that no consideration is being given by the art to the inactivation of virus for providing an RS virus vaccine. There is clear prejudice in the art against using such procedure. The applicants have found that, if the virus first is purified and then inactivated using β-propiolactone, ascorbic acid or octyl glucopypranoside, then a safe and effective vaccine preparation can be obtained, which in particular, elicits protective immune response without causing enhanced pulmonary pathology (immunopotentiation). For the following reasons, it is believed that applicant's claimed vaccine and method of preparation of the vaccine are patentable over the prior art cited by the Examiner.

The Examiner states in the Office Action that:

> "...claims 1 to 4, 15 and 16 remain rejected under 35 U.S.C. 103 over Downing et al in view of Bordt et al and further in view of McIntosh et al."

Reconsideration is requested having regard to the following discussion.

It is pointed out to the Examiner that the rejection as stated in the previous Office Action reads:

> "Claims 1 to 4, 15 and 16 are rejected under 35 U.S.C. 103 as being unpatentable over Bordt et al in view of Downing et al and further in view of

> McIntosh et al." (see page 8, first complete paragraph).

Accordingly, it is not clear whether the Examiner is substituting a new ground of rejection for the previous ground of rejection or is merely maintaining the previous ground of rejection with the identification of the primary reference inadvertently reversed. From the remarks that are made in the Office Action and the manner of presentation of the Examiner's argument, it would appear that the Examiner intends a new ground of rejection with the identification of the primary reference deliberately reversed. Applicant's remarks are made in such context, although the Examiner does state, with reference to the prior rejection that:

> "Applicant's arguments are not persuasive as stated in the previous Office Action."

The Examiner further states:

> Applicant argues the references individually and not their combination. One cannot show unobviousness by attacking references individually, where the rejections are based on a combination of references."

With reference to this comment, it is submitted that it is a necessary adjunct to considering a combination of references, to consider the individual teachings of such references in order to ascertain whether or not there is motivation to combine the teachings in a manner asserted by the Examiner and hence, whether or not there is a basis for rejection based upon the combination of prior art which is relied on. It is believed that applicant's consideration of the prior art individually, in response to the prior Office Action, was in this very context.

In the Office Action, the Examiner indicates that the Downing et al reference teaches purification of virus free from cellular and serum components and that Bordt et al teach

inactivation of "the virus" with ascorbic acid. The Bordt et al reference discloses a bovine respiratory syncytial virus inactivated with ascorbic acid, but the vaccine composition is not purified in any manner. It is clear from Example 1 of Bordt et al that the ascorbic acid is added to virus fluid to effect the inactivation and this virus fluid is not processed further in any way which would result in purification of the material.

The Examiner states that:

> "There was a expectation in the art regarding the use of inactivated virus before purifying the product in a vaccine composition is discussed by Downing et al (see page 216, para 1, lines 9-11)."

It is not clear where the Examiner finds support for this statement in lines 9 to 11 on page 216. The Examiner has quoted the passage from Downing et al as a whole, but nowhere does the passage refer to the expectation that is referred to by the Examiner. For emphasis, the passage as a whole reads:

> "one prerequisite for systematic biochemical and functional analysis of viruses is an abundant and very pure viral preparation, preferably one with infective virus particles. The efficient and effective purification schemes for enveloped viruses are important both clinically and for many research efforts especially for the development of strategies for disease intervention, particularly where traditional vaccines have not worked well. Respiratory syncytial virus (RSV) is an example of an enveloped virus from the class of paramyoxoviridae. RSV causes respiratory infection that is both difficult to treat and is not currently amenable to prevention by vaccination."

This passage clearly refers to the problems of a traditional vaccine strategy for RS virus infection and the need for the development of strategies for disease intervention, that is therapeutic treatment of infection, rather than prevention of the disease by vaccination, since it is indicated by Downing et al this is not possible by traditional means. The whole

thrust of Downing, therefore, is to provide an affinity purification method for RSV using a specific material to provide purified virus to carry out the studies which are referred to in the first paragraph of the Downing et al reference. Downing provides no motivation whatsoever to provide an inactivated RS viral preparation for vaccine use and, indeed, Downing et al indicates that traditional vaccination routes for RSV infection have not been successful.

The Examiner further states:

> "Formalin-inactivation caused disease potentiation partly due to the action on the F and G glycoproteins and impure viral preparation containing cellular or serum components (see page 3, para 3, lines 5-10 of the last Office Action)."

Applicants have reviewed the section to which the Examiner refers in the prior Office Action and can find no such statement. The applicants have also reviewed the remainder of the Office Action and further, can find no such statement. The basis of the Examiner's assertion, therefore, is obscure.

The Examiner further states:

> "Downing et al also addresses the issue why vaccines have not worked in the past partly due to impure viral preparation (see introduction section)."

Downing et al does not in any way address why vaccines have not worked in the past. What the introductory portion of the Downing et al reference states is that traditional routes of vaccination against RSV viral infection have not been successful and that it is necessary to produce pure viral preparation for the purpose of carrying out systematic studies on the virus with a view to the development of strategies for disease intervention. Downing et al does not in any way contemplate a traditional means of preventing disease by RS viral infection, since Downing et al and, indeed others in the art as noted by the above discussion of the prejudice in the

art simply did not believe that it would be possible to provide an inactivated RSV preparation which would be effective.

The Examiner further states:

> "One of ordinary skill in the art would be motivated to purify the virus first to remove contaminants as suggested by Downing et al then inactivate the virus with the ascorbic acid or other inactivating agent that has been used traditionally in the virology field. One of ordinary skill in the art would have expected that by purifying the virus first then inactivation of virus would be more efficacious since there is no contaminants."

It is submitted that there is no such motivation provided by the prior art. The only motivation provided by Downing et al is the provision of a process of purifying RS virus for the purpose of studying its biology for the purpose of the development of a strategy for disease intervention for a disease where traditional vaccination methods have been ineffective. The only motivation provided by Bordt is the realization that ascorbic acid may be used for inactivation of various viral preparations, one example of which is bovine RSV. However, the preparation of such inactivated materials does not involve any purification, as is evident from Example 1 of the Bordt et al reference.

Absent the hindsight of the present invention, there is absolutely no basis for the assertion made by the Examiner in the last paragraph of the above quotation. There is no suggestion whatsoever, in the prior art that has been relied on, that one would first purify the virus and then inactivate it with the expectation of obtaining a more efficacious vaccine.

The Examiner states that:

> "McIntosh was incorporated to as evidence that one of ordinary skill in the art would have been motivated and expected to inactivate 'human RSV' as

set forth in the first Office Action (see page 9, first paragraph).

While McIntosh et al teach that human RSV is the most important cause of viral lower respiratory tract disease in infants and children, and that human RSV is a paramyxovirus, it is not seen in what way these observations are relevant to the patentability of applicant's claims. It is not seen where, in the first paragraph on page 9 of the first Office Action, or indeed in the last Office Action, there is basis for the quotation "human RSV", as stated by the Examiner.

It is clear from the above comments that the applicants vaccine composition of claim 1 and method of immunizing defined in claim 15 are clearly patentable over the teachings of the combination of Downing et al, Bordt et al and McIntosh et al, however the references are ordered, and hence, the rejection of claims 1 to 4, 15 and 16, insofar as they remain in the application, under 35 U.S.C. 103 as being unpatentable over Downing et al in view of Bordt et al (or Bordt et al in view of Downing et al) and further in view of McIntosh et al, should be withdrawn.

The Examiner has maintained the rejection of claims 5 and 6 under 35 U.S.C. 103 as being unpatentable over Downing et al in view of Preston et al. Reconsideration of the rejection is requested for the following reasons.

Claim 5 defines a method of preparing an immunopotentiating vaccine composition capable of protecting a human host immunized therewith against disease caused by infection by respiratory syncytial virus by effecting a plurality of defined steps. These steps include growing RS virus on a continuous cell line of vaccine quality to produce a grown virus, harvesting the grown virus to produce a harvested virus, purifying the harvested virus under non-denaturing conditions to produce a purified virus free from

cellular and serum components, inactivating the purified virus with an inactivating agent to provide a non-infectious non-immunopotentiating and protective RS viral preparation and formulating the non-infectious, non-immunopotentiating and protective viral preparation as a vaccine. Claim 5 has been amended to incorporate claim 9, which has been deleted, and claim 10 correspondingly has been made dependent on claim 5.

The teachings of Downing et al and their relevance to applicant's invention are discussed above in connection with the first prior art rejection. As pointed out earlier, the Downing et al reference does not teach inactivating any virus with any inactivating agent and there is prejudice in the art against inactivating virus for the purpose of providing vaccine compositions in view of the problems associated with such inactivation using formalin, the most common inactivating agent used in the preparation of vaccines. The Downing et al reference describes a procedure for preparing pure RS viral preparation for the purpose, as already noted, of assembling knowledge of the basic biology of the virus for the development of strategies for disease intervention. The Downing et al reference says nothing about the preparation of vaccine compositions and, indeed, is concerned with an ultimate goal of a strategy for disease intervention because traditional vaccination does not work.

The purpose of the Preston study was to understand the immune response relating to the reduced resistance of subsequent RSV infections, by in-vitro studies aimed at inhibiting the proliferative T-cell response to inactivated RSV. The purpose of the β-propiolactone used in this study was to prepare inactivated RSV to be used only to stimulate the adult mononuclear cells for the purpose described above. While, as the Examiner states, Preston et al teaches that β-propiolactone is effective in inactivating RSV, nevertheless,

this disclosure provides no motivation whatsoever to inactivate a virus for a vaccine composition for the same reasons that the Bordt et al reference provides no motivation for inactivation of pure virus for vaccine preparation, since the Downing et al reference, in fact, points away from vaccination as a means of controlling RS viral infection and, in fact, is concerned with strategies for disease intervention and not vaccination.

In the absence, therefore, of any motivation in the art to effect the steps recited in applicant's claim 5, which involve purification of the harvested virus under non-denaturing conditions, it is submitted that applicants claims 5 and 6 are patentable over the applied art and hence, the rejection thereof under 35 U.S.C. 103 as unpatentable over Downing et al in view of Preston et al should be withdrawn.

The Examiner retained rejection of claims 5 and 9 under 35 U.S.C. 103 as unpatentable over Downing et al in view of White et al. Reconsideration of the rejection is requested for the following reasons.

As the Examiner notes, White et al teaches inactivation of RSV by treatment with ascorbic acid. The purpose of the study reported by White et al was to determine the in vitro effect of ascorbic acid on viruses and to use the inactivated virus as a reagent in serologic assays, and not for the production of inactivated RSV vaccine. The Examiner states that:

> "Applicants arguments are not commensurate with the claimed invention. The claimed invention is not drawn to inactivation as a vaccine."

The Examiner will note that claim 5 now has been amended in this respect and specifically refers to production of a vaccine.

The Examiner states:

> "Further in view of inactivation with ascorbic acid is useful for serological assays wherein this antibody-antigen reaction it would have been reasonable for one ordinary skilled in the art to expect to use ascorbic acid for vaccination wherein an antigen-antibody reaction takes place."

It is submitted that the study reported by White and on which the Examiner refers provides no basis for any expectation with respect to an antibody response in a host to which is administered the RS viral vaccine composition of the present invention.

The Examiner further states:

> "Furthermore, applicants arguments of not yielding a preparation free of cellular contaminants are not persuasive because the claimed invention is not commensurate with the scope of the claims. The claimed invention only recites virus "substantially" free from cellular and serum components."

In this regard, while not necessarily agreeing with the Examiner's position, applicants have amended claim 5 and also claim 1 to delete the term "substantially".

In White, the infected cells are grown in roller bottles, scraped, disrupted by a freeze-thaw cycle and further clarified by centrifugation. This procedure of virus purification would not yield a viral preparation free of cellular contaminants as required by applicant's claims.

As already pointed out above, the Downing et al reference provides no motivation whatsoever for consideration of inactivation of virus, whether purified or not, as a route to providing an effective RS virus vaccine, since the whole thrust of Downing et al is to provide a pure viral preparation for the purposes of assembling knowledge of the basic biology of the viruses and developments of strategies for disease intervention. Accordingly, the combination of art lacks any

motivation whatsoever, to use ascorbic or any other material for inactivation of purified RS virus.

Accordingly, it is submitted that claims 5 and 9 are patentable over the applied art and the rejection thereof under 35 U.S.C. 103 as unpatentable over Downing et al in view of White et al should be withdrawn.

The Examiner indicated that claims 5, 7 and 8 remain rejected under 35 U.S.C. 103 as unpatentable over Downing et al in view of Prince et al and Georgiades et al. Reconsideration is requested having regard to the following discussion.

The Downing et al reference and the motivation provided thereby have been discussed above. The Prince et al reference relates to the use of non-ionic detergents to sterilize blood plasma, so as to be free of active hepatitis virus. As was previously pointed out to the Examiner, hepatitis is a DNA virus belonging to the hepadnaviridae family of viruses, while RSV is a negative strand RNA virus belonging to the paramyxoviridae virus family. The conditions found suitable for inactivating viruses belonging to the hepadnaviridae family of viruses may not be suitable for viruses belonging to the paramyxoviridae family. In the Prince et al reference, it is recommended that a combination of a non-ionic detergent, alcohol or ether, or a mixture of both, be used to inactivate hepatitis viruses during plasma processing. Detergent alone is used in the present application to inactivate RSV.

The Examiner states that:

> "While it is true Prince et al teach inactivation of the hepatitis virus with non-ionic detergents ... since Downing et al suggest the use of non-ionic detergents including octyl glucoside for solubilization of viral preparation of VSV ... it would have been expected non-ionic detergents would

> have inactivated the RS virus for the preparation of vaccine composition."

In the section to which the Examiner refers in Downing et al, on page 218, it is stated that octyl glucoside was used to solubilize proteins from VSV (vesicular stomatitis virus) and the VSV G protein was isolated. It is unclear how this teaching leads to any expectation from the Prince et al disclosure that any non-ionic detergent may be used for inactivation of RS virus.

The Georgiades et al reference is concerned with a process for the purification of interferon alpha and to a method of enhancing the overall recovery of interfon alpha. The purpose of using the detergent in the reference was to eliminate virus contamination and not to produce inactivated viral preparations. The Examiner states:

> "Further while it is true that Prince et al teach inactivation of plasma hepatitis virus and Georgiades et al teach inactivation of contaminating viruses by non-ionic detergents respectively, one of ordinary skill in the art would have been motivated and expected to use non-ionic detergents when the virus is first purified as suggested by Downing et al."

It is submitted that there is absolutely no justification in the combination of prior art for this assertion. It has already been pointed out the manner in which the Downing et al reference specifically points away from the use of viral preparations as a means of controlling respiratory syncytial virus disease, the whole purpose of the preparation of the purified virus in Downing et al being to assemble knowledge of the basic biology of the virus and the development of strategies for disease intervention and not for any vaccine. The secondary references merely point to the potential for inactivating various viruses using non-ionic detergents and there is no motivation whatsoever contained in these teachings

to utilize a non-ionic detergent for the inactivation of RS virus following the steps of growing, harvesting and purifying the virus, as required by applicant's claim 5, nor is there any suggestion for subsequent formulation of the inactivated viral preparation as a vaccine, also as required by applicants claim 5.

Accordingly, it is submitted that claims 5, 7 and 8 are patentable over the applied art and the rejection thereof under 35 U.S.C. 103 as being unpatentable over Downing et al, Prince et al and Georgiades et al should be withdrawn.

The Examiner indicates that claims 5, 10, 12 and 13 remain rejected under 35 U.S.C. 103 as unpatentable over Ewasyshyn et al in view of Mbiguino et al. Reconsideration is requested having regard to the following discussion.

The Examiner will note that claim 12 has been rewritten in independent form and claim 13 is dependent thereon. Claim 12, as amended, recites a multiple step procedure for the preparation of a vaccine against disease caused by infection by respiratory syncytial virus.

The Ewasyshyn et al reference describes the production of purified surface glycoproteins of RSV and PIV-3. As was previously pointed out to the Examiner, the only similarity or relevance to the present invention is that both the present invention and Ewasyshyn et al describe growing and harvesting of RS virus. Thereafter, the processes diverge signficantly. In the present invention, the harvested whole virus is further processed through the steps of purification, inactivation and formulation, while Ewasyshyn et al then solubilize and isolate glycoproteins from the harvested virus. There is, of course, no teaching in Ewasyshyn et al of inactivation of virus because the Ewasyshyn et al procedure extracts the surface glycoproteins from the virus and is concerned solely with processing that extracted material.

The Mbiguino et al reference is concerned solely with a procedure for purifying RS virus and comparing the use of sucrose gradient purification with percol, renografin and metrizamide for purification. The protocol utilized by Mbiguino et al is illustrated diagramatically in Figure 1 of the reference. There is no inactivation step which is carried out in Mbiguino et al.

It is submitted that the combination of Ewasyshyn et al and Mbiguino does not disclose or suggest applicants method as defined in claim 5 and particularly, the method defined in claim 12. Claim 5 defines a method of preparing a non-immunopotentiating, vaccine composition capable of protecting a human host immunized therewith against disease caused by infection by RS virus. The combination of steps recited comprises growing and harvesting the virus, both of which steps are described in Ewasyshyn and Mbiguino. Applicants then purify the harvested virus under non-denaturing conditions to provide a purified virus free from cellular and serum components. The Examiner concedes:

> "The Examiner acknowledges Ewasyshyn et al does not teach of purifying the virus. However in view that Mbiguino et al teaches of a new method to obtain substantial amounts of purified RSV, one of ordinary skill in the art would have been motivated to use the method as set forth in Mbiguino et al."

There is no reason to apply the teachings of Mbiguino et al to Ewasyshyn et al since the purpose of Ewasyshyn is to produce purified surface glycoproteins of RSV and PIV-3 by extraction of the glycoproteins and subsequent purification of the extracted proteins. It is not clear why one would apply any teachings of Mbiguino et al to the clear and limited teaching of Ewasyshyn et al. The Examiner further comments:

> "Mbiguino et al teaches an inactivation by using non-ionic detergent conditions using a sucrose gradient."

Nowhere does Mbiguino et al refer to inactivation of the virus and, indeed, this would appear to be counter-productive to the procedure which is employed by Mbiguino et al, who is attempting to obtain purified virus preparations with high titres (see Summary). There is no description in Mbiguino et al of the "non-ionic detergent conditions" to which the Examiner refers.

Applicants have pointed out that the Mbiguino et al purification method is not for vaccine development. The Examiner states:

> "Applicants arguments are noted. However applicants arguments are not persuasive since the claims are not drawn to a vaccine but an immunogenic composition."

It is noted that applicants claims are directed to the preparation of vaccines, in their amended form, as discussed above. The Examiner further states:

> "Since this method [i.e., Mbiguino et al] preserves viral infectivity would be expected the composition would be immunogenic as the claimed invention recites."

The indication that preservation of viral infectivity also clearly demonstrates that there is no inactivation step described or contemplated by Mbiguino et al.

Following the purification step, applicants inactivate the purified virus with an inactivating agent to provide a non-infectious, non-immunopotentiating and protective RS viral preparation and then formulate the non-infectious, non-immunopotentiating, protective RS viral preparation as a vaccine. Neither Ewasyshyn et al nor Mbiguino et al suggest any such inactivation and formulation steps.

In claim 12, the purification step is defined as a combination of microfiltration to remove cell debris, tangential flow ultrafiltration to remove serum components and provide a retentate, pelleting the retentate by ultracentrifugation to further remove serum components and then subjecting the pelleted material to sucrose gradient centrifugation. It is submitted that this specific combination of steps is not taught or suggested by the prior art. Claim 12 also recites the inactivation of the purified virus with an inactivating agent which is selected from the group consisting of β-propiolactone, a non-ionic detergent which is n-octyl-α-D-glycopyranoside or n-octyl-β-D-glycopyranoside and ascorbic acid. It is submitted that not only is inactivation not disclosed in either reference, but also none of the specific materials recited in claim 12 are described or suggested for such purpose in the applied combination of prior art.

Accordingly, it is submitted that claims 5, 10, 12 and 13 in their amended form, are patentable over the applied art and the rejection thereof under 35 U.S.C. 103 as unpatentable over Ewasyshyn et al in view of Mbiguino et al, should be withdrawn.

The Examiner refers to applicants traverse of the rejection of claim 11 over Ewasyshyn et al in view of Mbiguino et al and further in view of McIntosh et al and Paradiso et al. The Examiner indicates that the prima facie case of obviousness is maintained, but does not specifically recite a ground of rejection. If a ground of rejection is retained, applicants request reconsideration for the following reasons.

Claim 11 differs from claims 5 and 10 in reciting utilization of a VERO cell line as the continuous cell line of vaccine quality.

It was previously conceded to the Examiner that the McIntosh and Paradiso et al references both describe the use of VERO cells for growing RS virus. However, it has already been pointed out the manner in which the combination of Ewasyshyn et al and Mbiguino et al is deficient with respect to potential rejection of claim 5 and that none of these deficiencies is made up by the McIntosh and Paradiso et al references. In particular, it is submitted that the combination that has been made in no way discloses or suggests applicants specific combination of process steps as defined in claim 5. Accordingly, it is believed that claim 11 is patentable over the art. To the extent that there may be an outstanding rejection in this regard, it is submitted that the rejection of claim 11 under 35 U.S.C. 103 as being unpatentable over Ewasyshyn et al in view of Mbiguino et al and further in view of McIntosh et al and Paradiso et al, the rejection should be withdrawn.

The Examiner similarly refers to applicants traverse of the rejection of claim 14 over Ewasyshyn et al view of Downing et al and Kuchler. However, the Examiner does not recite any particular ground of rejection in the Office Action. Claim 14 has been amended to be in independent form and further to incorporate therein the subject matter of claim 10. If any ground of rejection remains, reconsideration is requested.

The disclosure of the Ewasyshyn reference has been discussed above. As noted herein and as conceded by the Examiner, the Ewasyshyn et al reference does not disclose purification of the virus and hence it cannot describe applicant's specific combination of process steps for such purpose recited in claim 14. Such process steps include microfiltration to remove cell debris, tangential flow ultrafiltration to remove serum components, gel filtration to

further remove serum components and ion-exchange chromatography to additionally remove serum components. In addition, the Ewasyshyn et al reference fails to recite or suggest inactivation of RS virus, nor the formulation of inactivated RS virus as a vaccine composition. The Ewasyshyn et al reference is solely concerned with the isolation and purification of specific glycoproteins from the RS virus.

The Downing et al reference, it is submitted, adds nothing to the Ewasyshyn et al reference other than the provision of a purified form of the RS virus. The purpose for generation of this material by Downing et al has been discussed in some detail above in connection with the rejection which is based on Downing et al. It is considered unnecessary to repeat those discussions here. Suffice it to say that the preparation of the purified RS virus in Downing et al was for the purpose of assembling knowledge of the basic biology of the virus and development of strategies for disease intervention. Downing et al does not describe or suggest any inactivation step, as already conceded by the Examiner.

In the Office Action, the Examiner indicates that the Kuchler teachings have been described in the prior Office Action. In this regard, the prior Office Action recites:

> "Kuchler teaches that there are three basic steps to the purification of viruses (p. 184-194). The first is clarification (p.185). The second is concentration which may be performed by several methods including ultrafiltration (p.185). The third step is purification. Kuchler teaches that purification of viruses may be accomplished by chromatograph and ion-exchange resins, by molecular sieving on gel filtration columns, by countercurrent distribution or by gradient centrifugation (p.186, paragraph 4)."

The Kuchler reference, therefore, simply contains a general teaching of the steps involved in purification of viruses and describes the use of various materials for purification. It

is submitted that this disclosure falls far short of applicants recited combination of process steps in claim 14, as discussed above.

As already pointed out, the combination of Ewasyshyn and Downing is deficient in failing to disclose or suggest an inactivation step and formulation of the inactivated virus as a vaccine and the Kuchler reference provides no remedy to this particular defect.

Accordingly, it is apparent that claim 14 is patentable over the art. With respect to any specific rejection that may be considered to exist, it is submitted that claim 14 is not open to rejection under 35 U.S.C. 103 as being unpatentable over Ewasyshyn et al in view of Downing et al and Kuchler.

Although the Examiner repeated the prior art rejections from the prior Office Action, it is noted that the Examiner did not specifically indicate that the Office Action of November 26, 1996 was Final, either by checking the appropriate box on the Office Action Summary, or by specific statement in the Office Action. Accordingly, it is considered that the rejection is a non-final rejection, although the prior art rejections are repeated.

Having regard to the revisions made to the claims and the discussion above with respect to each of the grounds of rejection, it is submitted that the claims of this application are patentable over the applied prior art and that the application is in an allowable form.

Should the Examiner consider that further revisions to the claim language are required to place the application in an allowable form, the Examiner is urged to contact the applicants representative, Mr. Michael Stewart, collect, at the number given below, with a view to arriving at mutually acceptable language.

It is believed that this application now is in condition for allowance and early and favourable consideration and allowance are respectfully solicited.

Respectfully submitted,

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